# EQUAL RISK FOR EQUAL MEASURES? CARDIOVASCULAR DISEASE, BLOOD PRESSURE, AND LIPIDS

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# OUTLINE

- Surrogate Endpoint Definition

- Blood Pressure
  - Epidemiology
  - Clinical Trials
  - Modeling

- Cholesterol
  - Epidemiology
  - Clinical Trials
  - Modeling

- Equivalent Treatments

# OUTLINE

- ALLHAT
- Subgroups
- Is relationship linear?
- How much change is needed? And for how long?
- Surrogate's status is treatment dependent
- Conclusions

# Surrogate Endpoint - Prentice Criteria

**A response variable for which a test of the null hypothesis of no relationship to the treatments under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint**

1. **Surrogate must be a correlate of true clinical outcome**

2. **Surrogate must fully capture the net effect of treatment on clinical outcome**

# Operational advantages

1. Length of time

2. May be easier to measure

3. Smaller sample size

# BLOOD PRESSURE

## EPIDEMIOLOGY

## LANCET, 1990, MCMAHON ET AL.

### Epidemiology

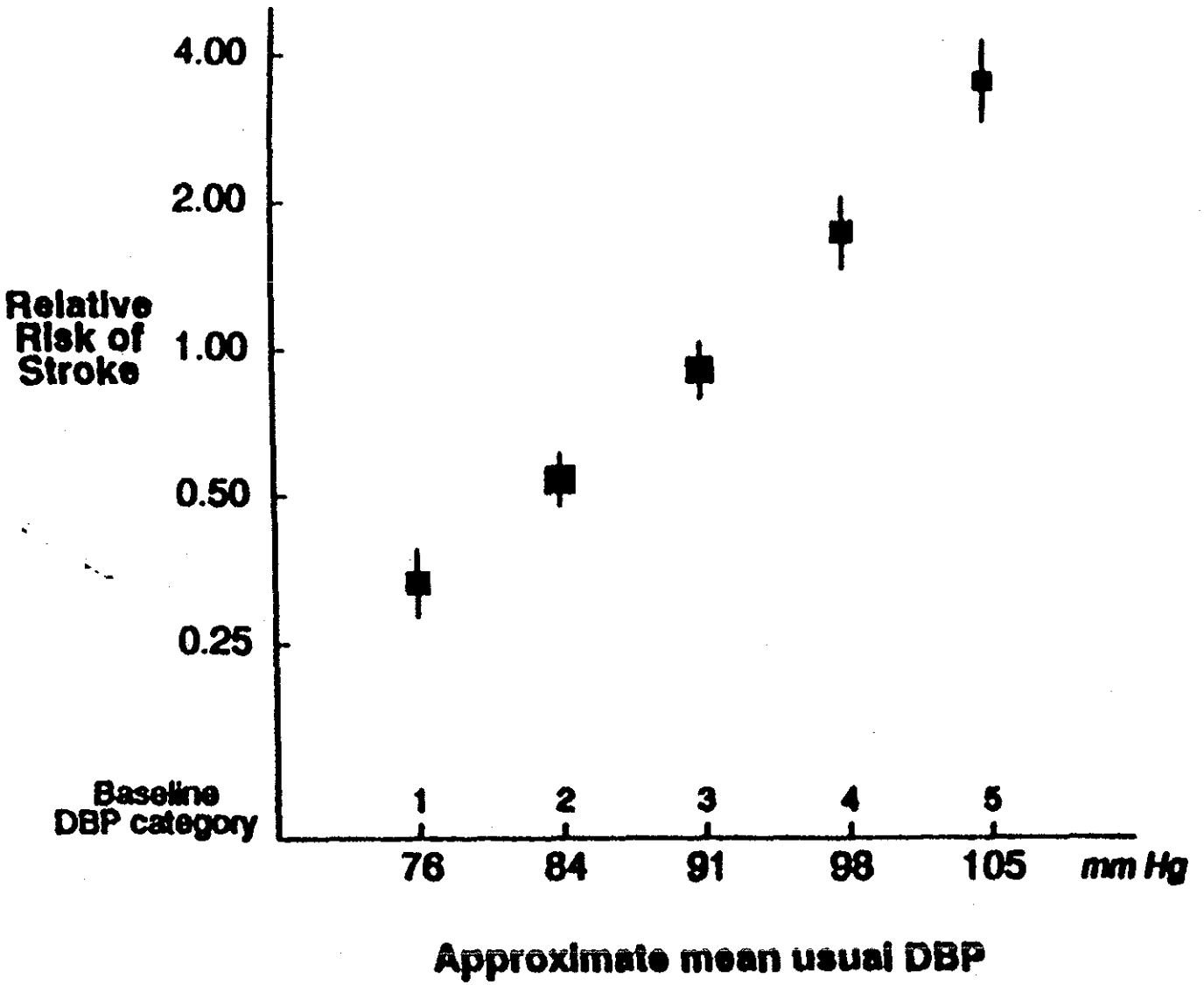
5-6 mm Hg decrease in DBP

35-40% decrease in stroke incidence

20-25% decrease in CHD incidence

## Stroke and usual DBP

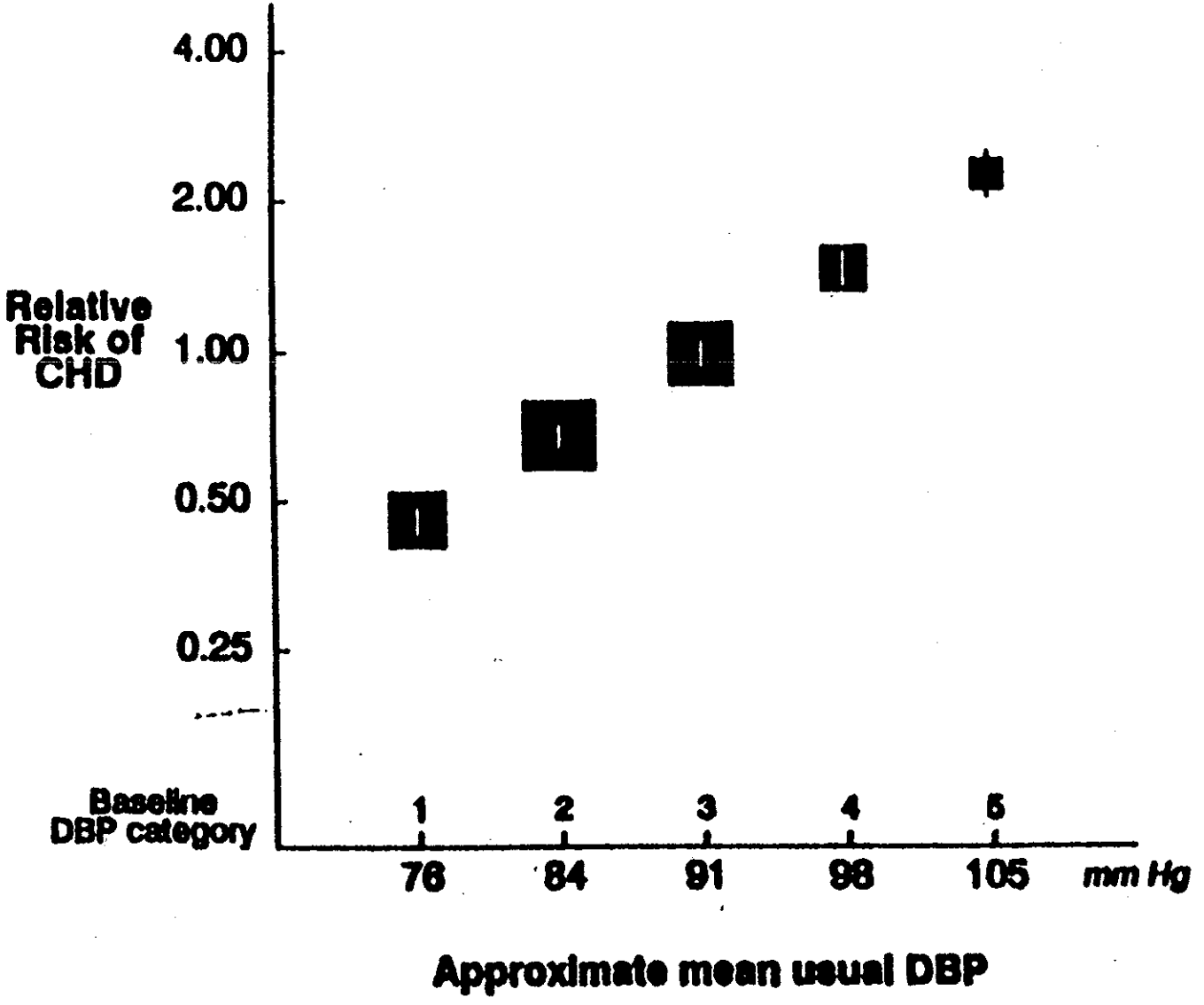
(in 5 categories defined by baseline DBP)
7 prospective observational studies: 843 events



## Coronary Heart Disease and usual DBP

(in 5 categories defined by baseline DBP)

9 prospective observational studies: 4856 events



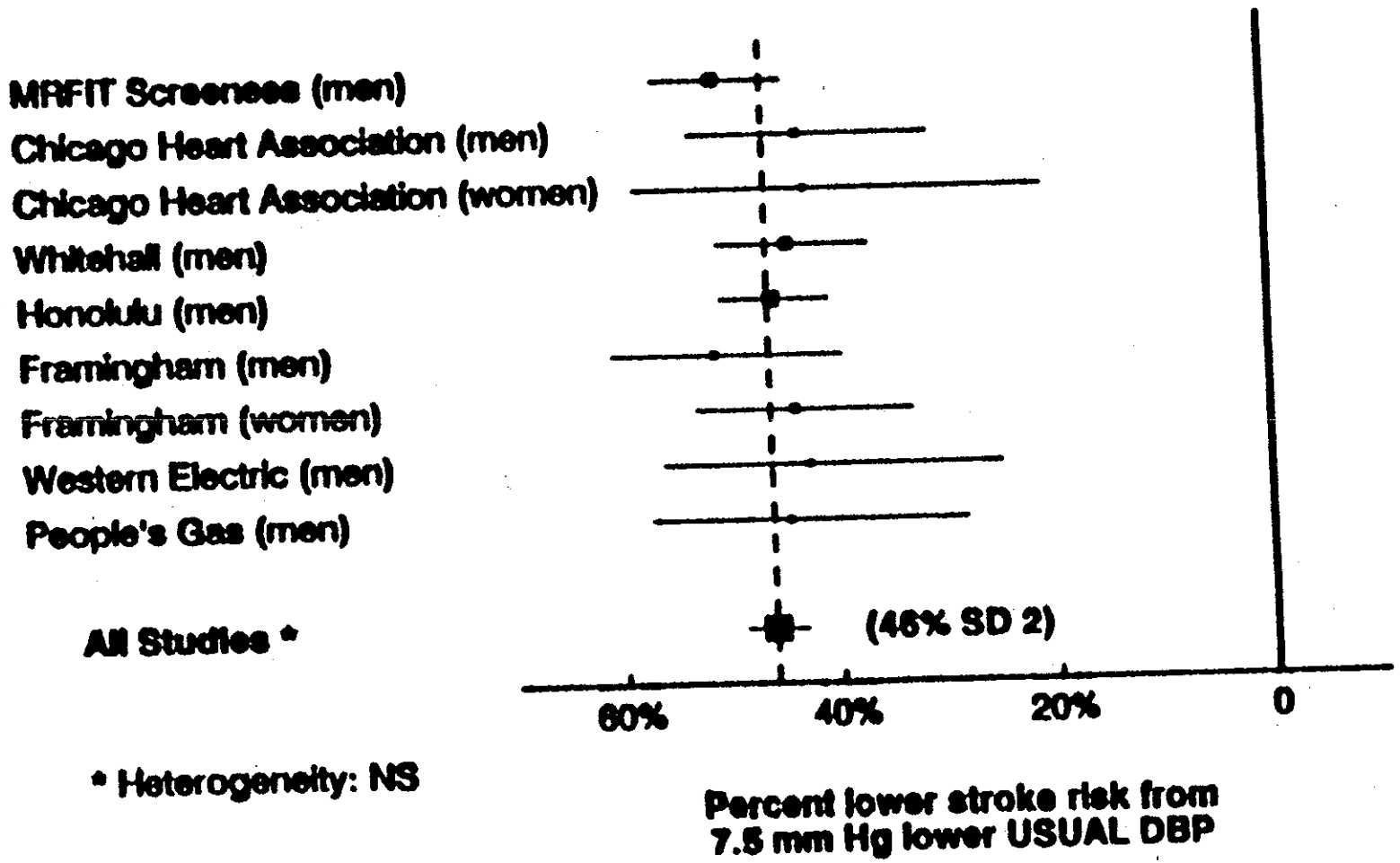



**Fig 3—Estimates from seven studies of eventual difference in stroke risk associated with about a 7·5 mm Hg lower usual DBP.**

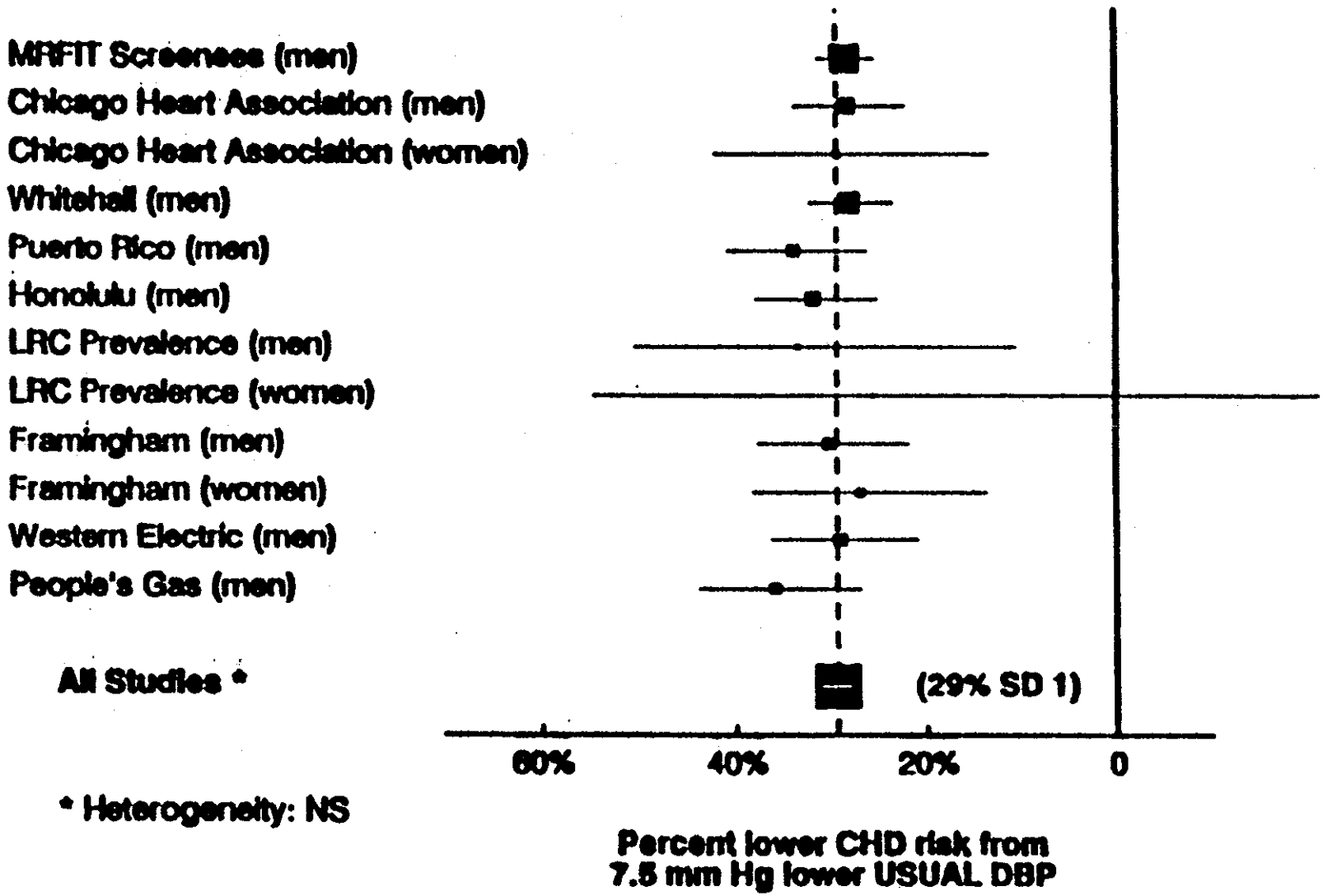



**Fig 5—Estimates from nine studies of eventual difference in coronary heart disease risk associated with about a 7·5 mm Hg lower usual DBP.**

# BLOOD PRESSURE

## CLINICAL TRIALS

## LANCET, COLLINS ET AL., 1990

**Stroke incidence decreased by 42%**
**(100% of expected result)**

**CHD incidence decreased by 14%**
**(~50% of expected result)**

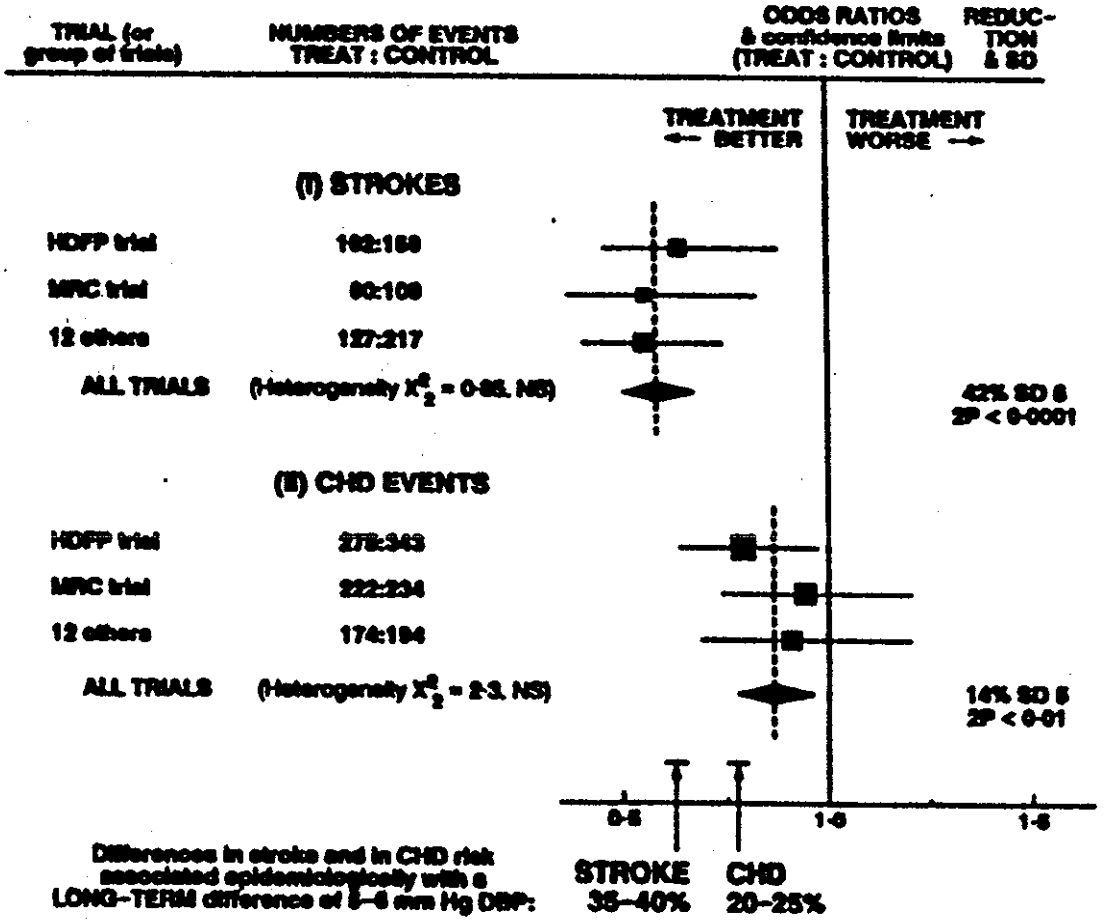
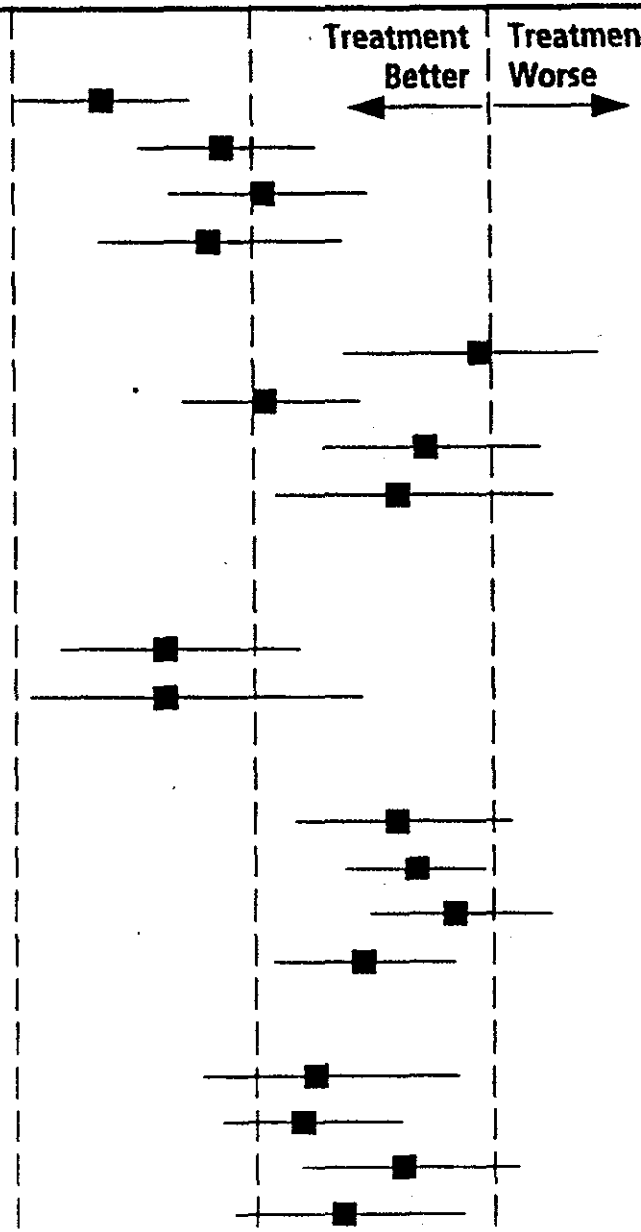



**Fig 2—Reduction in the odds of stroke and of CHD in the HDFP trial, the MRC trial, and in all 12 other smaller unconfounded randomised trials of antihypertensive therapy (mean DBP difference 5–6 mm Hg for 5 years).**

| Outcome<br>Drug<br>Regimen | Dose | No. of Trials | Events, Active Treatment/ Control | RR (95% CI) |
|---|---|---|---|---|
| **Stroke** | | | | |
| Diuretics | High | 9 | 88/232 | 0.49 (0.39-0.62) |
| Diuretics | Low | 4 | 191/347 | 0.66 (0.55-0.78) |
| Beta-blockers | | 4 | 147/335 | 0.71 (0.59-0.86) |
| HDFP | High | 1 | 102/158 | 0.64 (0.50-0.82) |
| **Coronary Heart Disease** | | | | |
| Diuretics | High | 11 | 211/331 | 0.99 (0.83-1.18) |
| Diuretics | Low | 4 | 215/363 | 0.72 (0.61-0.85) |
| Beta-blockers | | 4 | 243/459 | 0.93 (0.80-1.09) |
| HDFP | High | 1 | 171/189 | 0.90 (0.73-1.10) |
| **Congestive Heart Failure** | | | | |
| Diuretics | High | 9 | 6/35 | 0.17 (0.07-0.41) |
| Diuretics | Low | 3 | 81/134 | 0.58 (0.44-0.76) |
| Beta-blockers | | 2 | 41/175 | 0.58 (0.40-0.84) |
| **Total Mortality** | | | | |
| Diuretics | High | 11 | 224/382 | 0.88 (0.75-1.03) |
| Diuretics | Low | 4 | 514/713 | 0.90 (0.81-0.99) |
| Beta-blockers | | 4 | 383/700 | 0.95 (0.84-1.07) |
| HDFP | High | 1 | 349/419 | 0.83 (0.72-0.95) |
| **Cardiovascular Mortality** | | | | |
| Diuretics | High | 11 | 124/230 | 0.78 (0.62-0.97) |
| Diuretics | Low | 4 | 237/390 | 0.76 (0.65-0.89) |
| Beta-blockers | | 4 | 214/410 | 0.89 (0.76-1.05) |
| HDFP | High | 1 | 195/240 | 0.81 (0.67-0.97) |



# BLOOD PRESSURE

## MODELING

- DBP/SBP correlate of stroke, CHD

- HDFP - Hardy, Hawkins - AJE, 1983

Total Mortality
All - 65% of effect
captured by follow-up BP indices
(SBP, DBP, at DBP goal, on BP Rx)

Stratum I - 33% of effect captured

- SHEP- unpublished

Stroke
36% of effect captured by
follow-up SBP

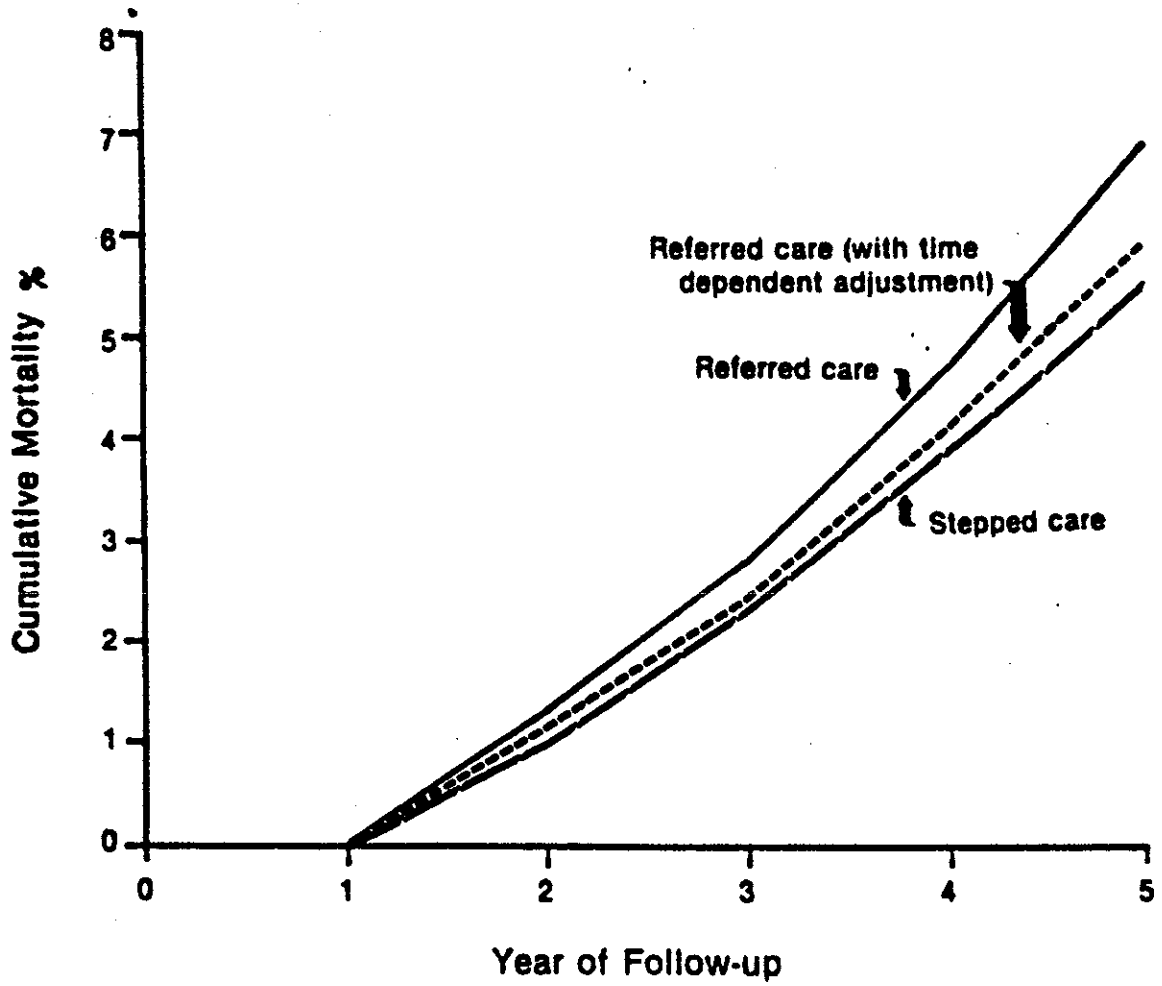



FIGURE 2. Cumulative mortality beyond one year for all participants in the Hypertension Detection and Follow-up Program, adjusting for sex, race, age, end organ damage, smoking status, diastolic blood pressure (BP), systolic BP, and antihypertensive medication status at baseline with adjustment for the time-dependent covariates of diastolic BP, medication status, systolic BP, and diastolic BP goal at one, two, and four years.

# CHOLESTEROL

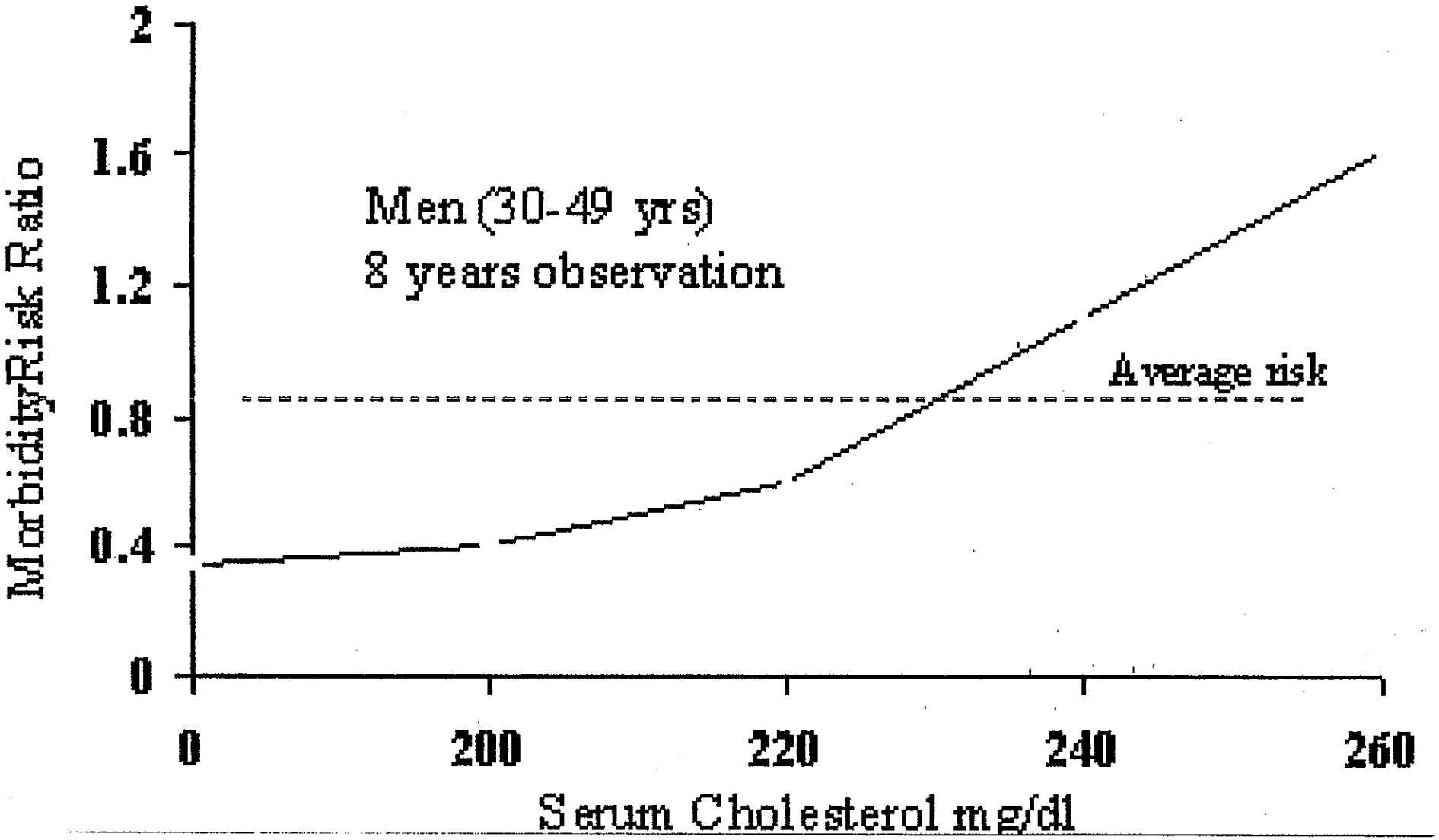
## EPIDEMIOLOGY

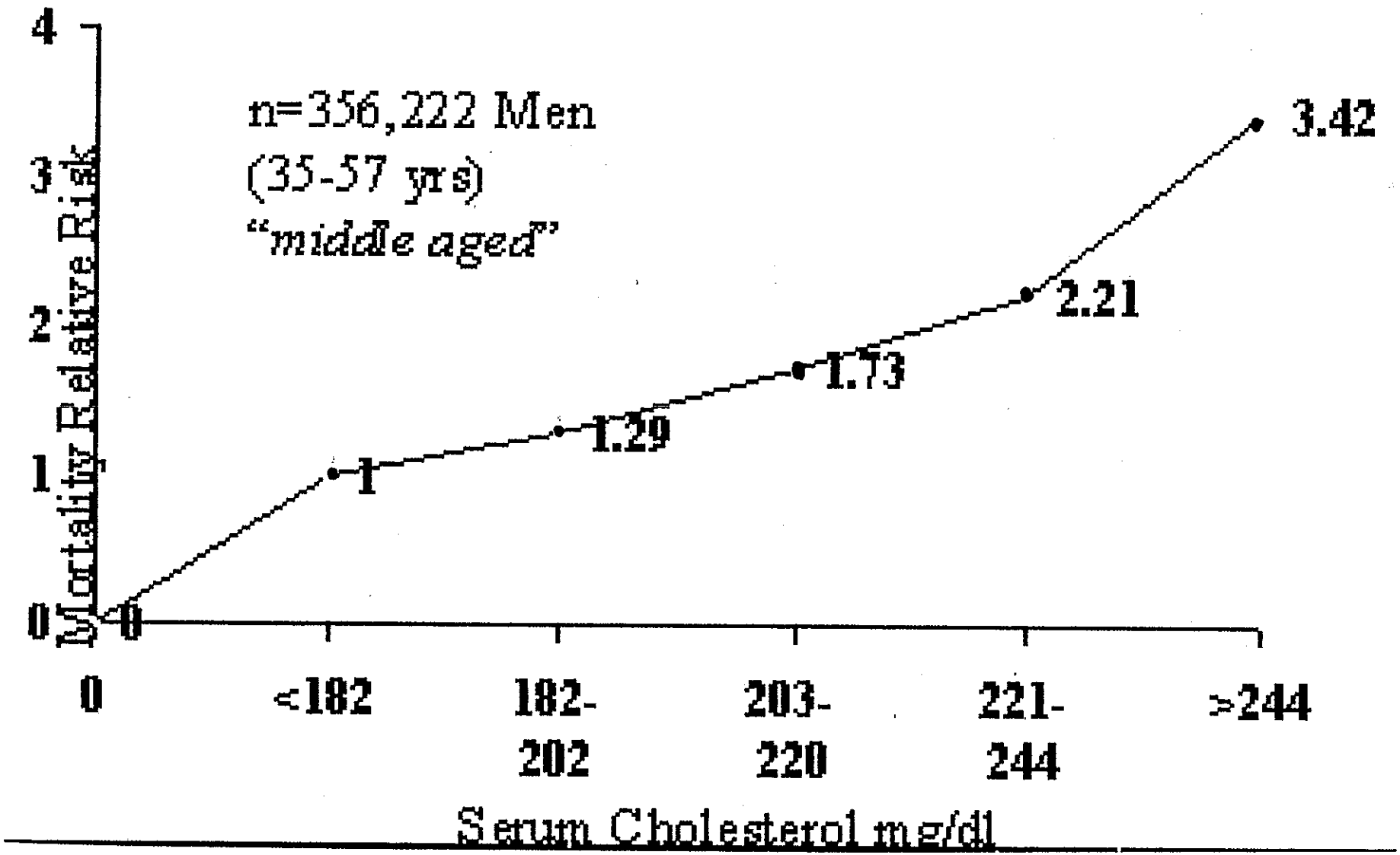
## FRAMINGHAM

10 mg/dl decrease in total cholesterol associated with 10- 20% decrease in CHD incidence

## MRFIT

10 mg/dl decrease in total cholesterol associated with 10-15% decrease in total mortality


Morbidity Risk Ratio
2
1.6
1.2
0.8
0.4
0
Men (30-49 yrs)
8 years observation
Average risk
0
200
220
240
260
Serum Cholesterol mg/dl


4
3
2
1
0
Mortality Relative Risk
n=356,222 Men
(35-57 yrs)
"middle aged"
3.42
2.21
1.73
1.29
1
0
0
<182
182-202
203-220
221-244
>244
Serum Cholesterol mg/dl

# CHOLESTEROL

## CLINICAL TRIALS

### DJ Gordon's Meta-Analysis Table

### Statins

**CHD incidence decreased by 30%**
**(100% of expected result)**

**Total mortality decreased by 22%**
**(100% of expected result)**

### Non-statins

**CHD incidence decreased 17%**

**Total mortality increased by 1%**

## Table 2: Cholesterol-Lowering Trials -- By Intervention Class

| Intervention | # Trials | # Treated | Person-Yrs | Mean Cholesterol Reduction |
|---|---|---|---|---|
| Pre-Statin: | | | | |
| Surgery | 1 | 421 | 4084 | 22% |
| Resins | 3 | 1992 | 14491 | 9% |
| Niacin | 2 | 1264 | 7365 | 8% |
| Diet | 6 | 1200 | 6356 | 11% |
| Fibrates | 7 | 9669 | 50333 | 9% |
| Hormones | 3 | 1301 | 4031 | 11% |
| Sub-Total | 22 | 15847 | 86660 | 10% |
| Statins** | 12 | 17405 | 72879 | 20% |
| Statins (published) | 11 | 12893 | 61599 | 28% |
| Total*** | 34 | 33252 | 159539 | 15% |
| Total (published) | 33 | 28740 | 148259 | 17% |

## Table 2: Cholesterol-Lowering Trials -- By Intervention Class

| Intervention | # Trials | Mean Cholesterol Reduction | Percent Change in Risk* | | | |
|---|---|---|---|---|---|---|
| | | | Mortality | | | CHD |
| | | | Total | CHD | Non-CHD | Incidence** |
| Pre-Statin: | | | | | | |
| Surgery | 1 | 22% | -24% | -30% | -7% | **-43%** |
| Resins | 3 | 9% | -11% | -32% | 33% | **-21%** |
| Niacin | 2 | 8% | -4% | -7% | 8% | **-17%** |
| Diet | 6 | 11% | -6% | -21% | 0% | **-24%** |
| Fibrates | 7 | 9% | 3% | -8% | **32%** | **-18%** |
| Hormones | 3 | 11% | **18%** | 5% | **77%** | 7% |
| Sub-Total | 22 | 10% | 1% | **-9%** | **24%** | **-17%** |
| Statins** | 12 | 20% | **-22%** | **-29%** | **-11%** | **-30%** |
| Statins (published) | 11 | 28% | **-20%** | **-33%** | -3% | **-33%** |
| Total*** | 34 | 15% | **-10%** | **-17%** | 5% | **-24%** |
| Total (published) | 33 | 17% | **-6%** | **-16%** | **13%** | **-23%** |

* Statistically significant results are indicated in boldface type.

** Combined incidence of CHD death and nonfatal myocardial infarction.

*** Includes unpublished preliminary data from LIPID.

# CHOLESTEROL

## MODELING

-Total/LDL/HDL/Triglycerides
correlate of stroke, CHD,Total Mortality

- CARE - Sacks et al. , Circ, 1998

CHD (+CABG/PTCA)
- 72% accounted for by LDL
- 83% by LDL + Trig.
- 87% by LDL + Trig. + HDL

- WOSCOPS - CHD events, Circ., 1998

CHD events fit on Framingham

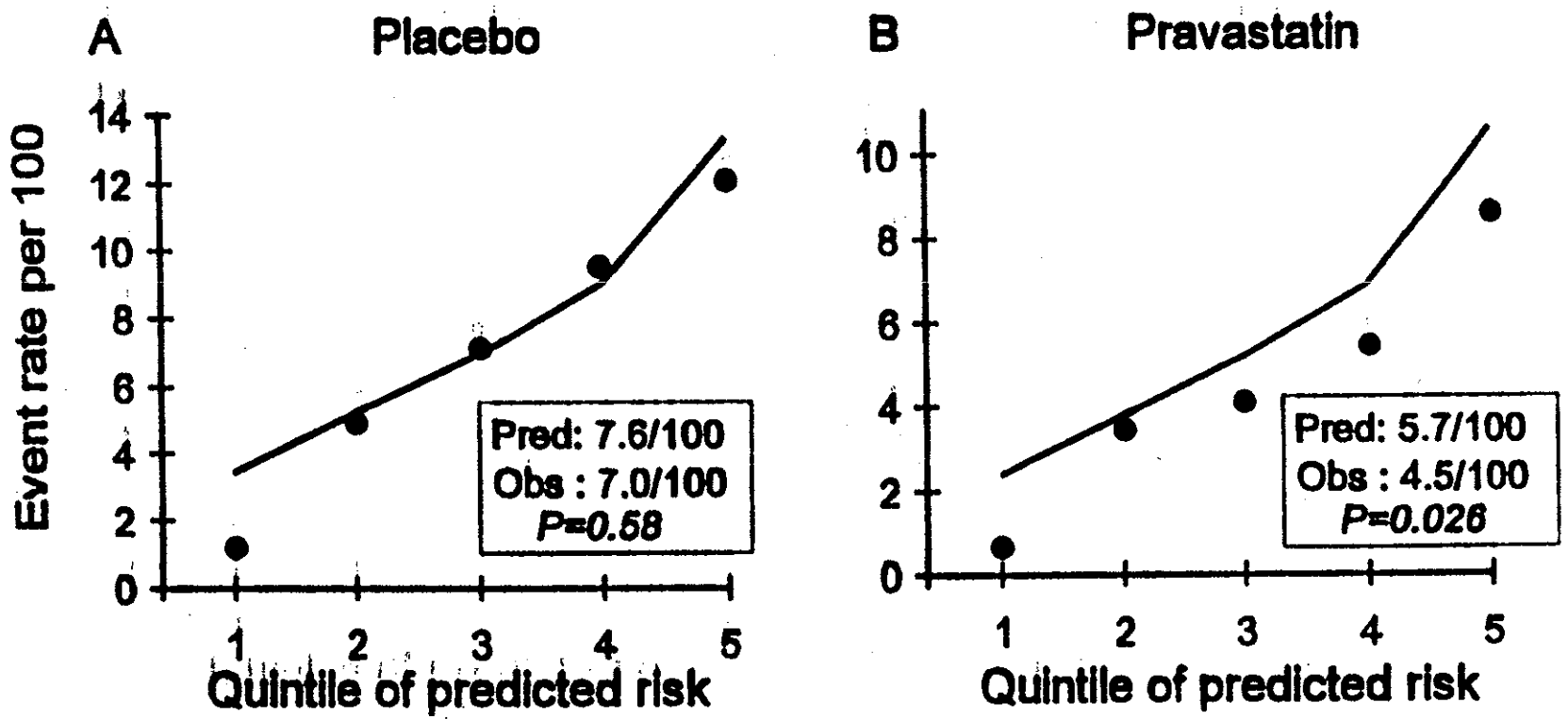



**Figure 4.** Framingham analysis. Predicted risk over 4.4 years for each subject was derived from Framingham risk equation.[17]

# Equivalent Treatments

**In terms of what?**

- **BP reduction or**
  **CHD/Stroke/Total Mortality**

- **Lipid reduction (TC, LDL, Trig.)/**
  **increase (HDL [HIT?]) or**
  **CHD/Stroke/Total Mortality**

**Equivalent in SUBGROUPS?**

- **Women (HIT Trial)**
- **African-Americans**
- **Diabetics**
- **Elderly**

# Surrogate Endpoints

**Is there equal risk for equal blood pressure?**

- **Overviews of hypertension trials --> antihypertensive treatment yields ↓ CHD event rates**
- **Reduction is less than expected based upon epidemiological data**
- **Possible explanation - adverse effects of drugs, particularly diuretics, offset potential benefit of BP ↓**
- **New BP drugs - CCB's, ACE inhibitors, α-blockers are approved for use in BP ↓**
- **New agents are more costly. Evidence with regard to clinical outcomes is limited.**

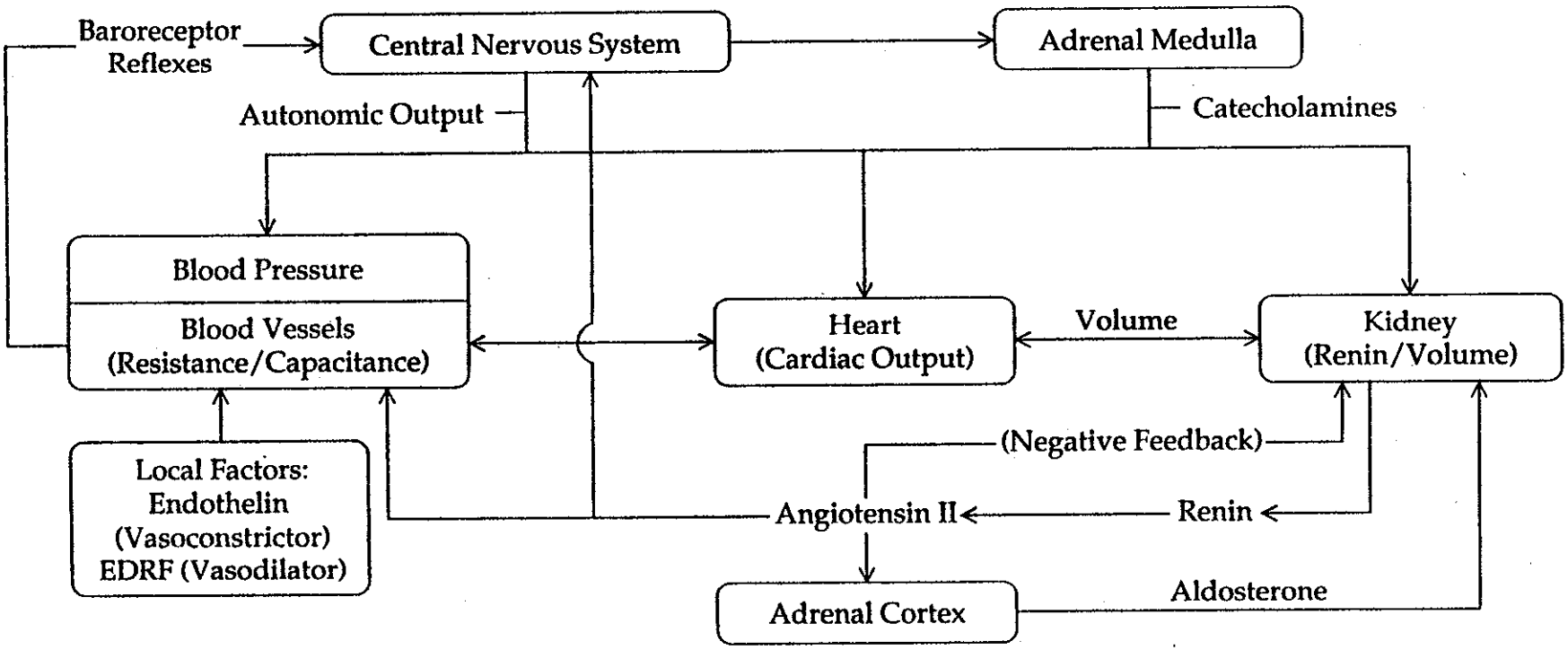



*Figure 1* **A series of feedback loops (of which the major ones are shown) regulate blood pressure.**

# Possible Mechanisms for Proposed Differential Effects of Antihypertensive Drugs on CHD

*Diuretics*

Increased LDL cholesterol, glucose, insulin, uric acid
Potassium/magnesium depletion
Early improvement of LV mass

*ACE inhibitors*

Antiproliferative effects
Prevention of unfavorable vascular remodeling
Enhanced fibrinolysis

*Calcium antagonists*

Reduced lipid and calcium accumulation
Anti-ischemic effects
Negative inotropic effect

*Alpha-1 antagonists*

Improved lipid profile
Reduced insulin resistance
Enhanced fibrinolysis

# ALLHAT

## Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

A practice-based randomized clinical trial sponsored by NHLBI, composed of two trials

- Antihypertensive component - to determine whether newer antihypertensive agents (ACE inhibitor, calcium channel blocker, alpha blocker) reduce incidence of CHD compared to a diuretic

- Cholesterol-lowering component - to determine whether reduction of serum cholesterol reduces all-cause mortality in moderately hypercholesterolemic patients

# Eligibility Criteria for AHT

- Men and women ≥ 55 years
- SBP 140-180 mm Hg and/or
  DBP 90-110 mm Hg
- High risk - at least one of
  LVH, diabetes, ASCVD (MI, stroke, PVD),
  low HDL, smoking

# Eligibility Criteria for LLT

- In AHT
- LDL 120-189 mg/dl
  (or 100-129 mg/dl with CHD)
- Triglycerides < 350 mg/dl

# ALLHAT Trial Design
# (AJH, Davis et al., 1996)

- Randomized, multicenter clinical trial
- 42,515 participants in AHT
- Assignment to 1 of 4 BP drugs
  double-blind
- Subset of 10,312 in LLT
- Assignment to LL drug or usual care
  unblinded
- Primary Endpoint
  AHT - CHD death + nonfatal MI
  LLT - Total mortality
- Follow-up: 4.2-8 years (6 yr mean)

# Is relationship linear?

## Blood Pressure

HDFP - J-shape - Cooper et al., AJH, 1990
HOT - Lancet, 1998

## Cholesterol

Grundy - Circ., 1998
Sacks et al. - Circ., 1998

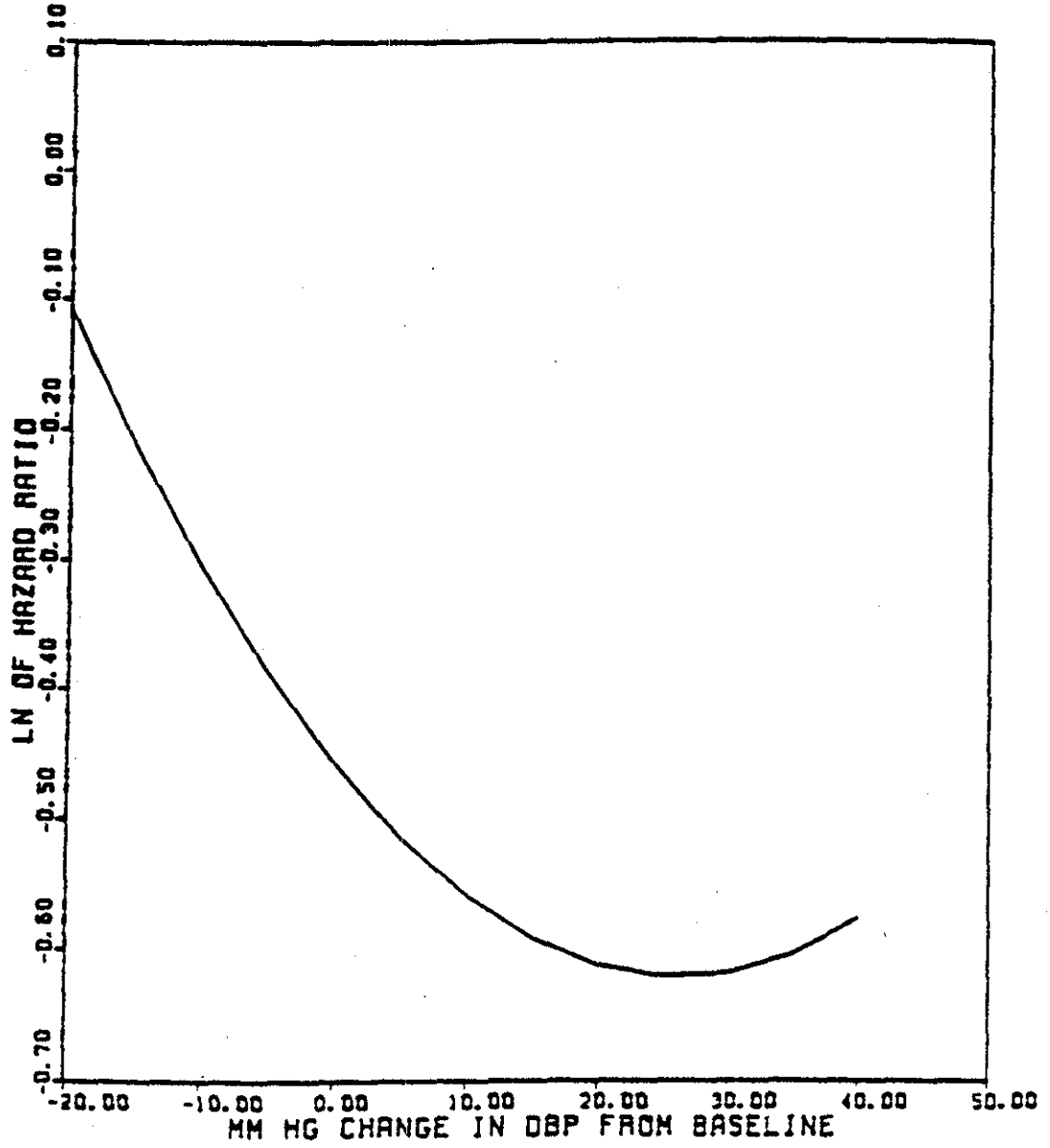
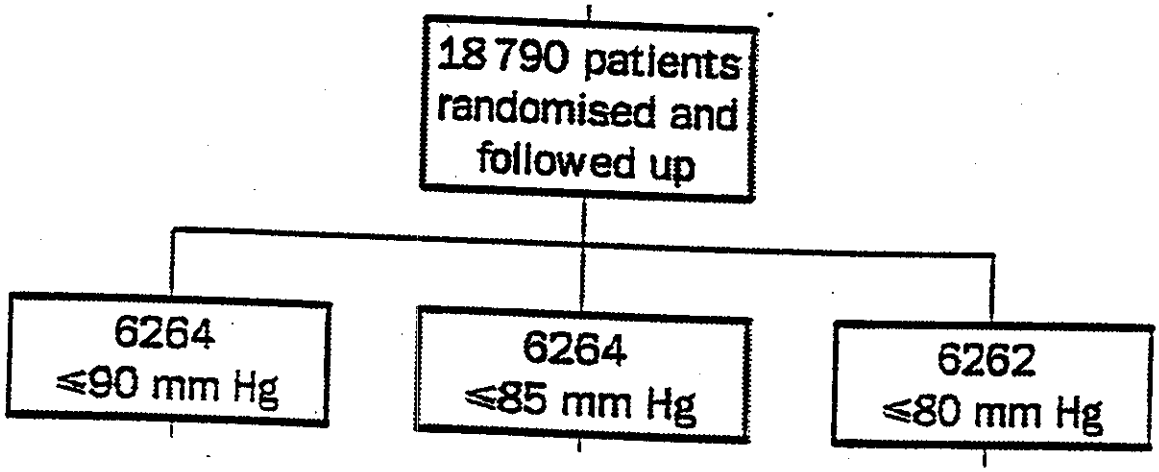



FIGURE 2. Theoretical plot of final time-dependent Cox model based on diastolic blood pressure (DBP) for entire population, Hypertension Detection and Follow-up Program, 1973–1979.

# HYPERTENSION OPTIMAL TREATMENT (HOT) RANDOMIZED TRIAL



# HYPERTENSION OPTIMAL TREATMENT (HOT) RANDOMIZED TRIAL

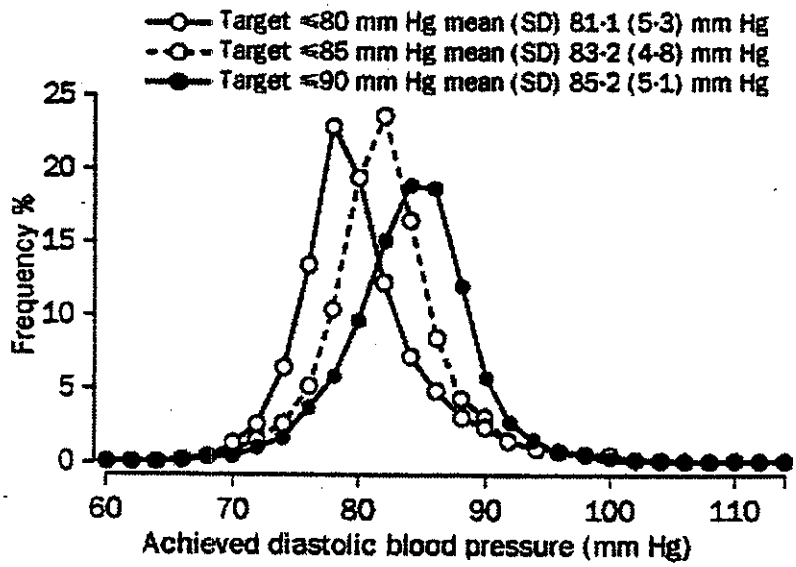



Figure 2: **Distribution of mean diastolic blood pressures from 6 months' follow-up to the end of the study**

# HYPERTENSION OPTIMAL TREATMENT (HOT) RANDOMIZED TRIAL

| Event | Number of events | Events/ 1000 patient-years | p for trend | Comparison | Relative risk (95% CI) |
|---|---|---|---|---|---|
| **Major cardiovascular events** | | | | | |
| ≤90 mm Hg | 232 | 9·9 | | 90 *vs* 85 | 0·99 (0·83-1·19) |
| ≤85 mm Hg | 234 | 10·0 | | 85 *vs* 80 | 1·08 (0·89-1·29) |
| ≤80 mm Hg | 217 | 9·3 | 0·50 | 90 *vs* 80 | 1·07 (0·89-1·28) |

# HYPERTENSION OPTIMAL TREATMENT (HOT) RANDOMIZED TRIAL

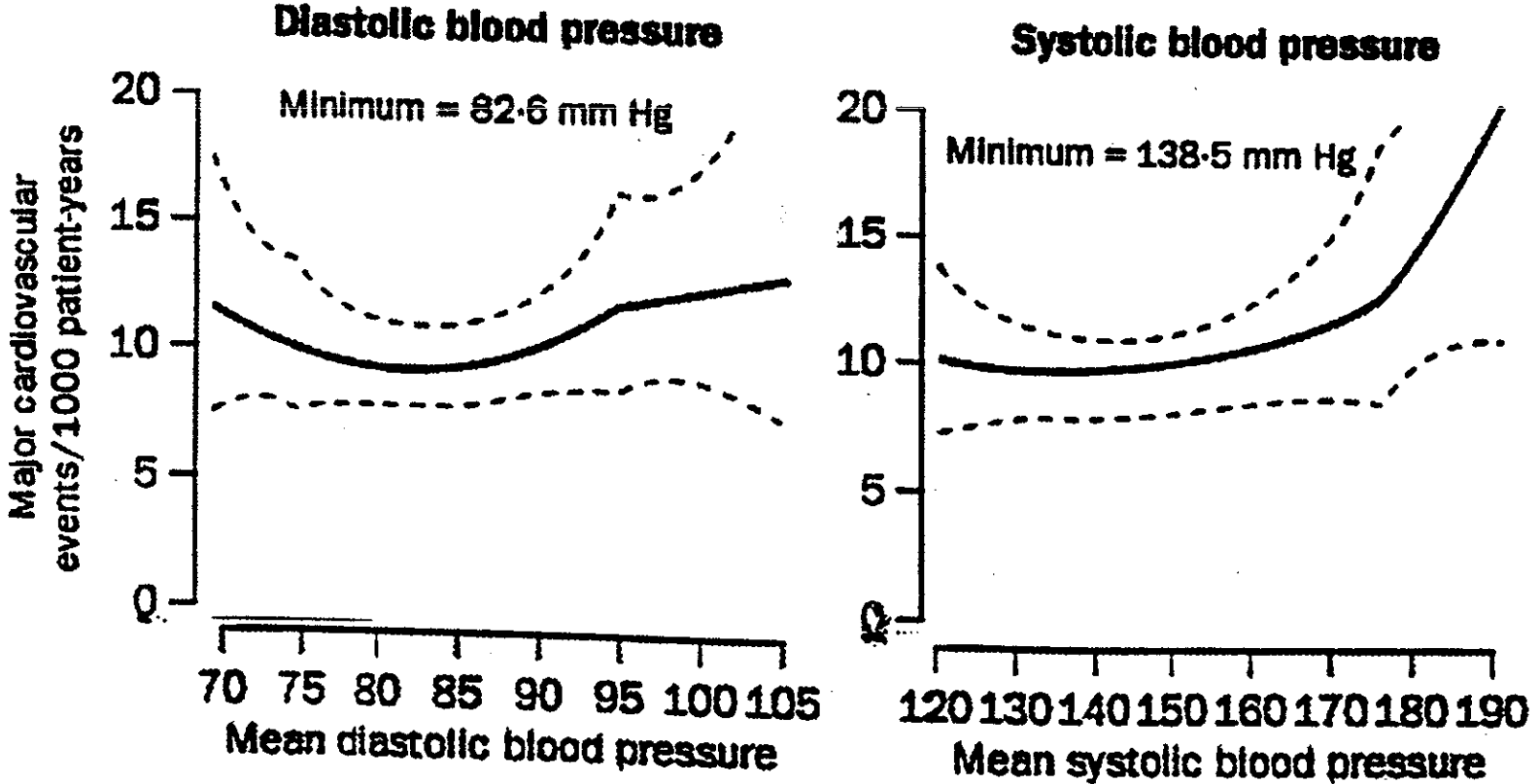



Figure 3: **Estimated incidence (95% CI) of cardiovascular events in relation to achieved mean diastolic and systolic blood pressure**

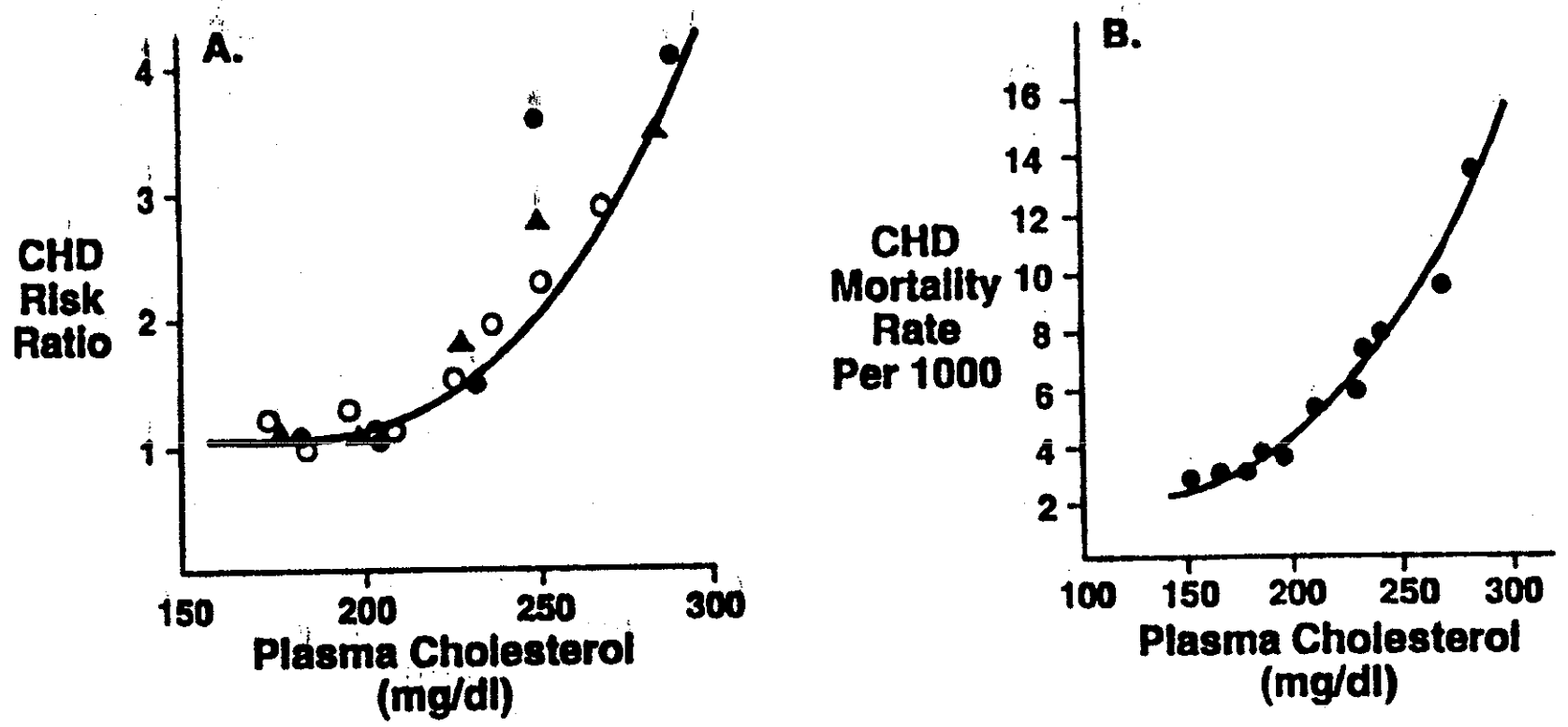



**Figure 1.** Relationship between serum cholesterol levels and CHD in male subjects without established CHD at entrance into prospective study. Fig 1A relates serum cholesterol levels to relative risk (risk ratio) for developing clinical CHD in earlier prospective studies: Framingham Heart Study[10] (●), Pooling Project[11] (▲), and Israeli Prospective Study[12] (○).

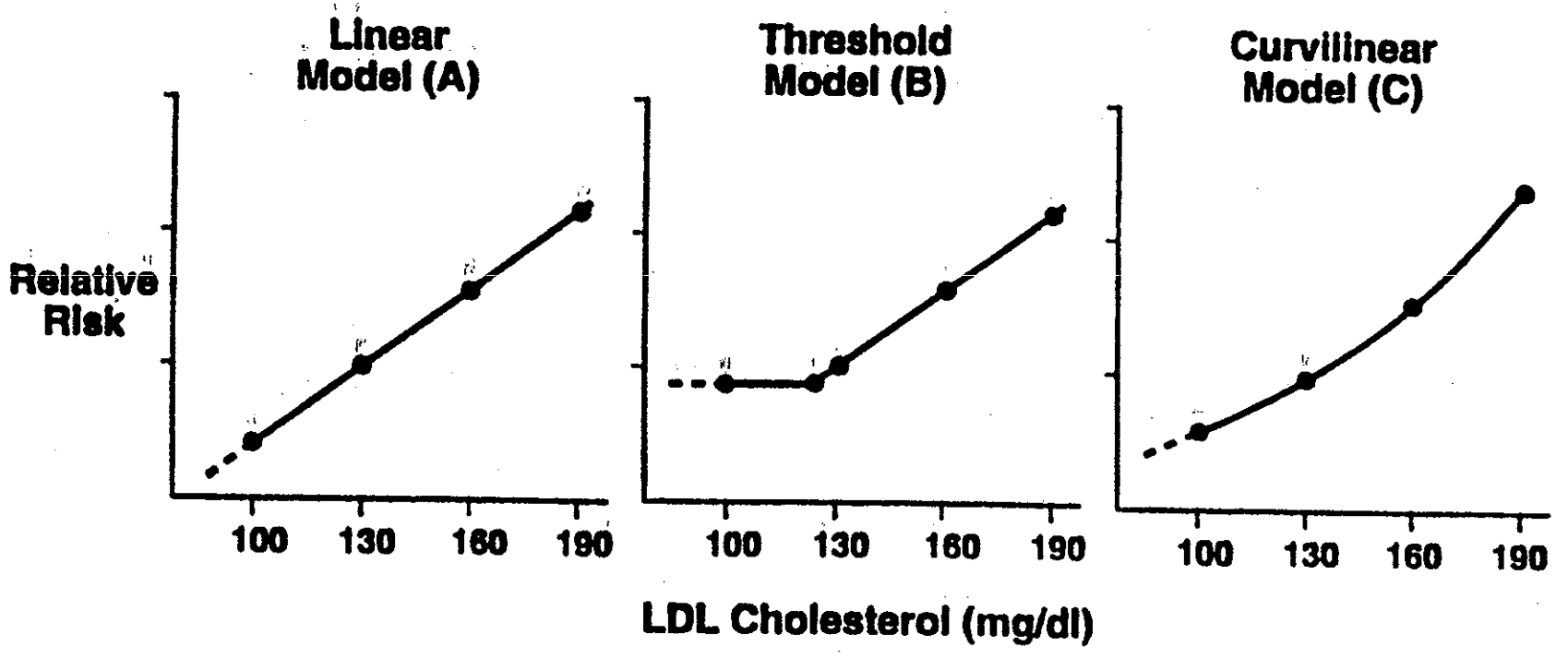



**Figure 2.** Theoretical models for effects of reducing serum LDL cholesterol concentrations on relative risk for recurrent coronary heart disease. Model A shows linear relationship; model B, threshold relationship; and model C, curvilinear relationship.

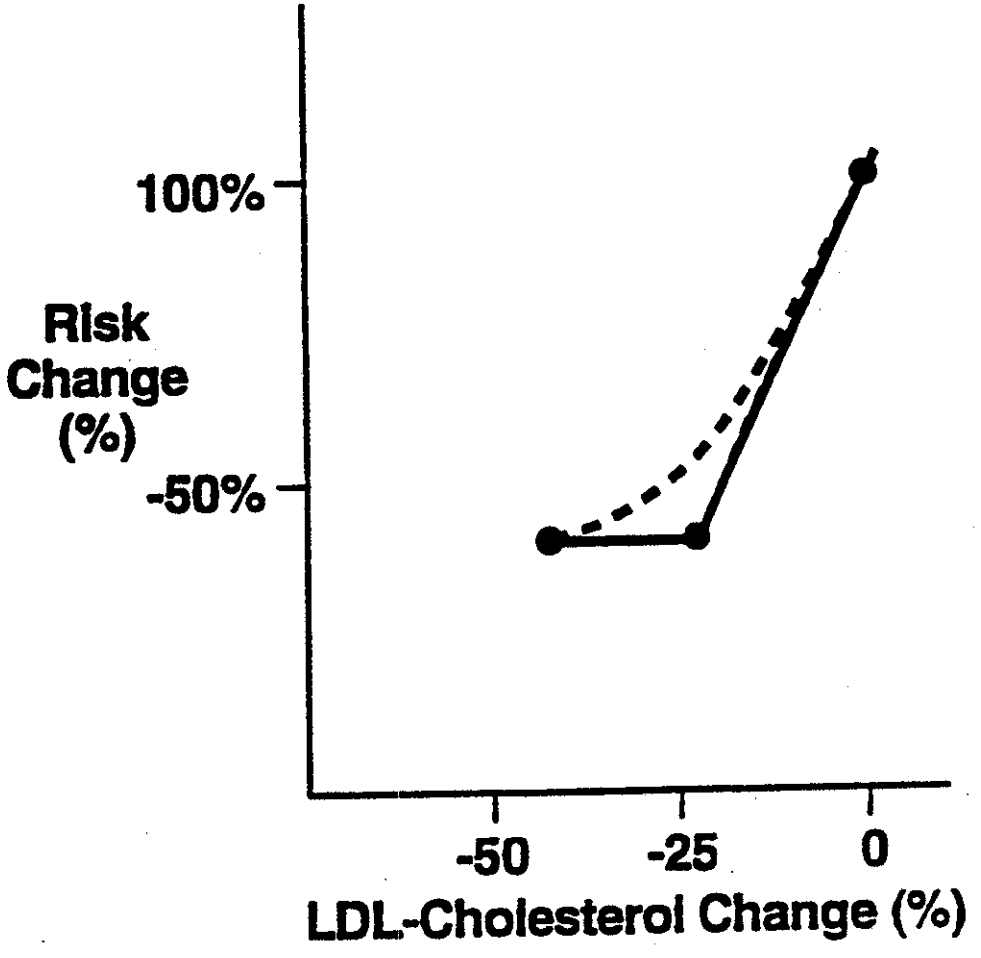
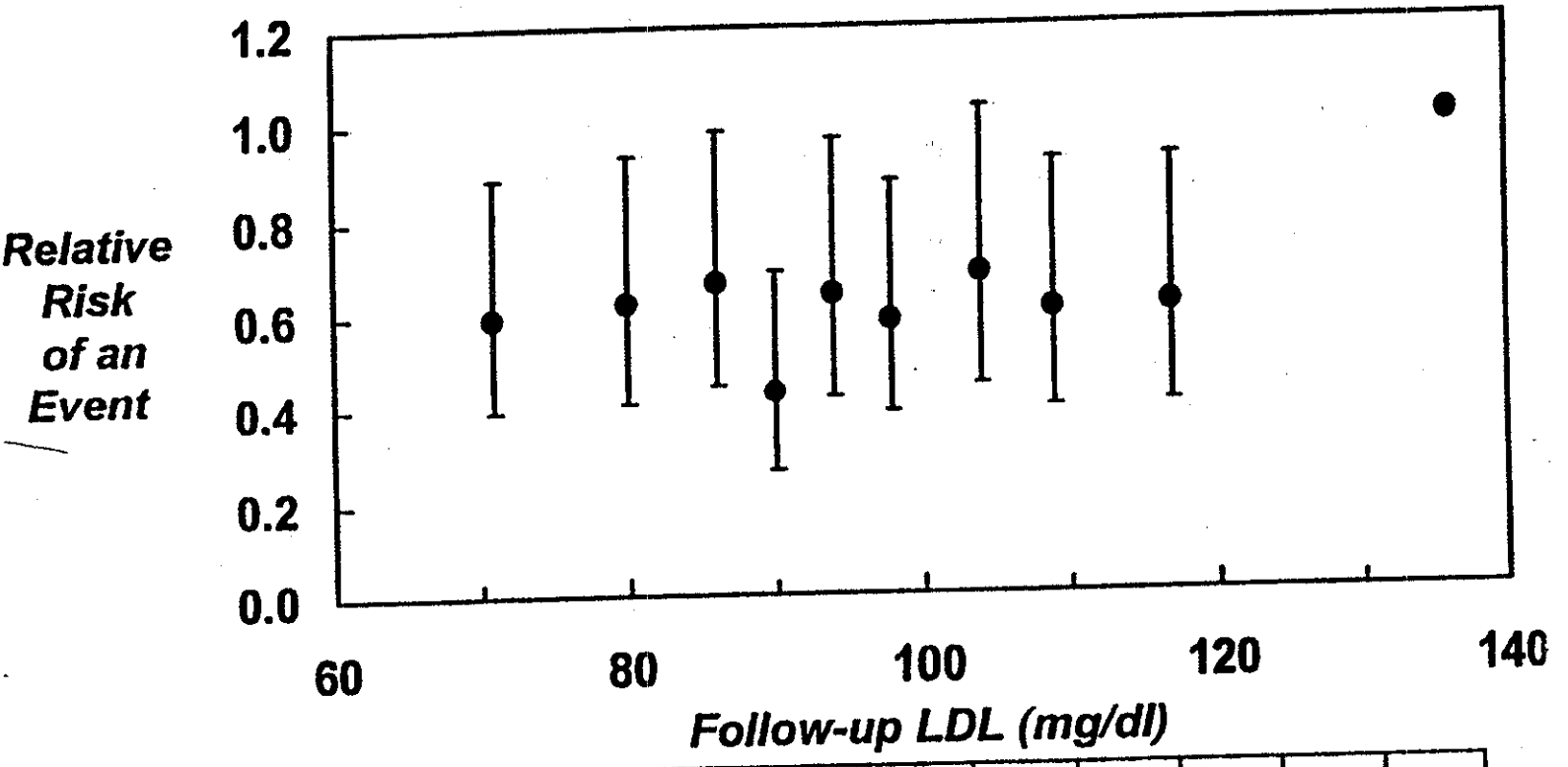



**Figure 3.** Observed relationship (solid line) between percentage reduction in LDL cholesterol levels and percentage reduction in major coronary events in WOSCOPS.[9] A threshold relationship was observed, although authors acknowledge that a curvilinear relationship (dashed line) could not be entirely ruled out.[9]

# Expanded Endpoint Pravastatin Group




| Decile # | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Median follow-up LDL | 71 | 80 | 86 | 90 | 94 | 98 | 104 | 109 | 117 | 136 |
| % LDL decrease | 43 | 38 | 35 | 33 | 31 | 30 | 26 | 25 | 21 | 9 |

**Figure 4.** LDL cholesterol concentration during follow-up and coronary events. Pravastatin group, n=2081 patients. Expanded end point: coronary death, nonfatal MI, CABG, or PTCA (430 patients with end point, 52 in 10th decile).

# How much change is needed?
# And for how long?

## Blood Pressure

### SHEP - JAMA, 1991

Change in BP, Stroke incidence

Ischemic Stroke incidence

## Cholesterol

### CARE - NEJM, 1996

Change in LDL, CHD incidence

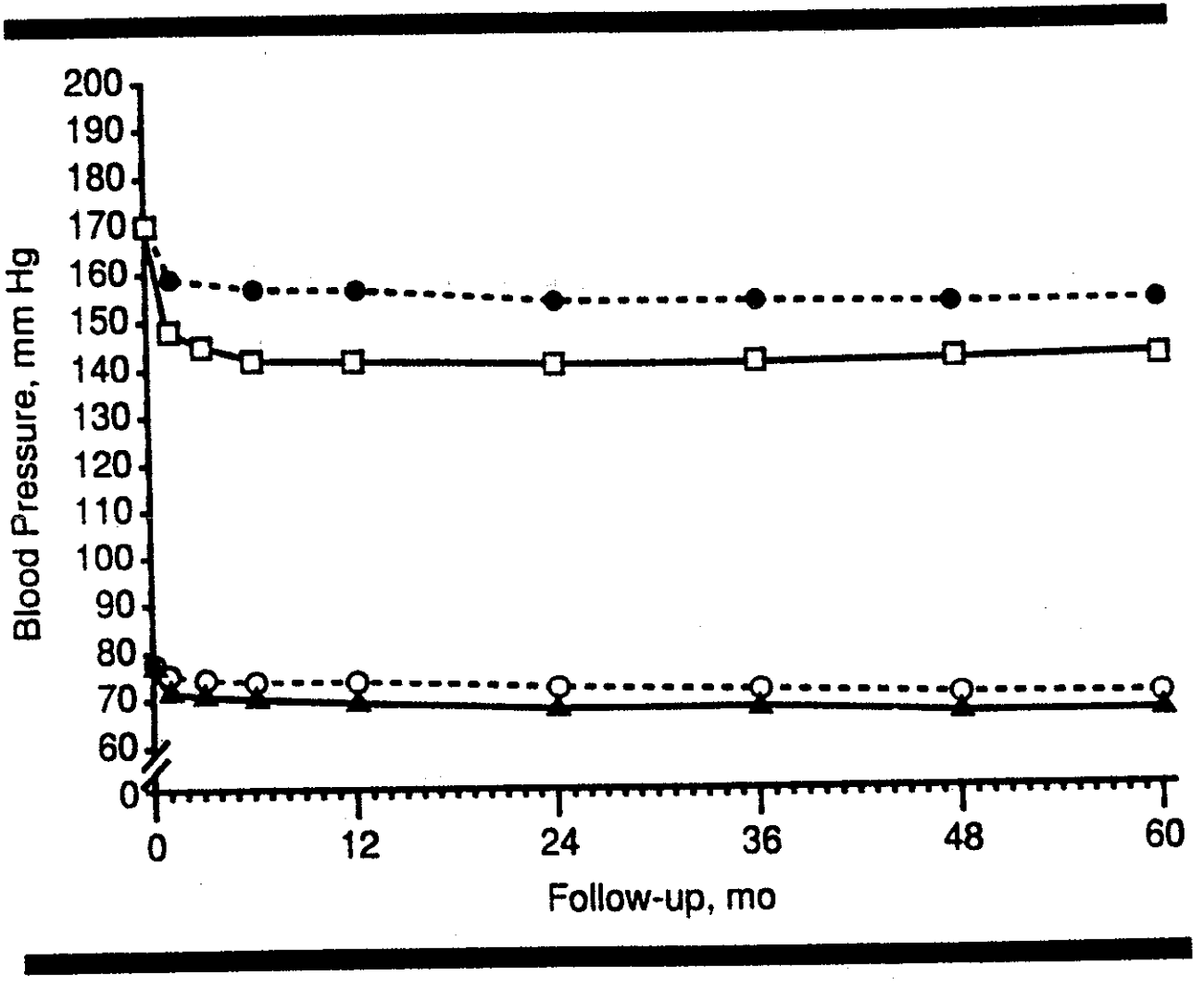



Fig 1. - Average systolic and diastolic blood pressure during the Systolic Hypertension in the Elderly Program follow-up plotted at 1, 3, 6, and 12 months and yearly therafter.

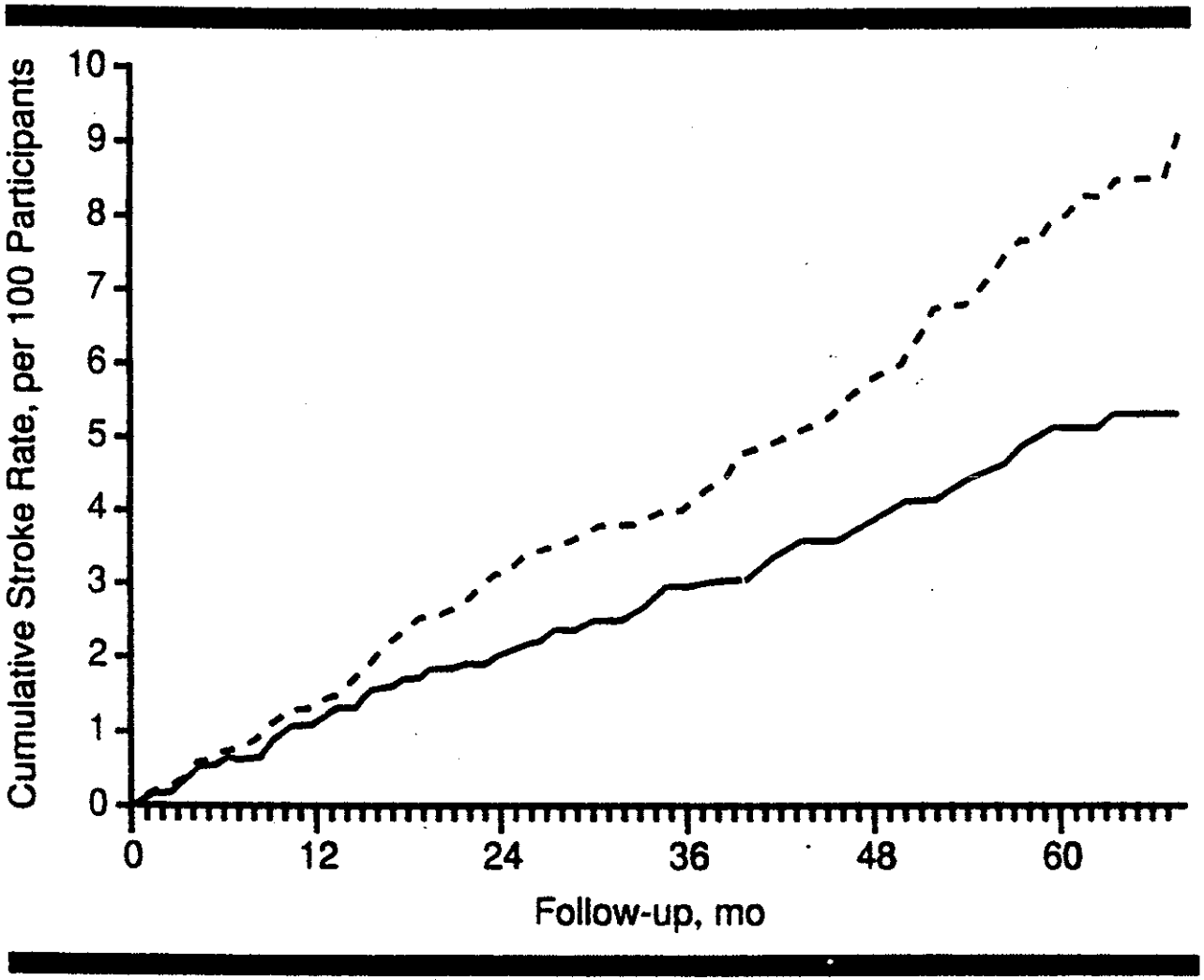
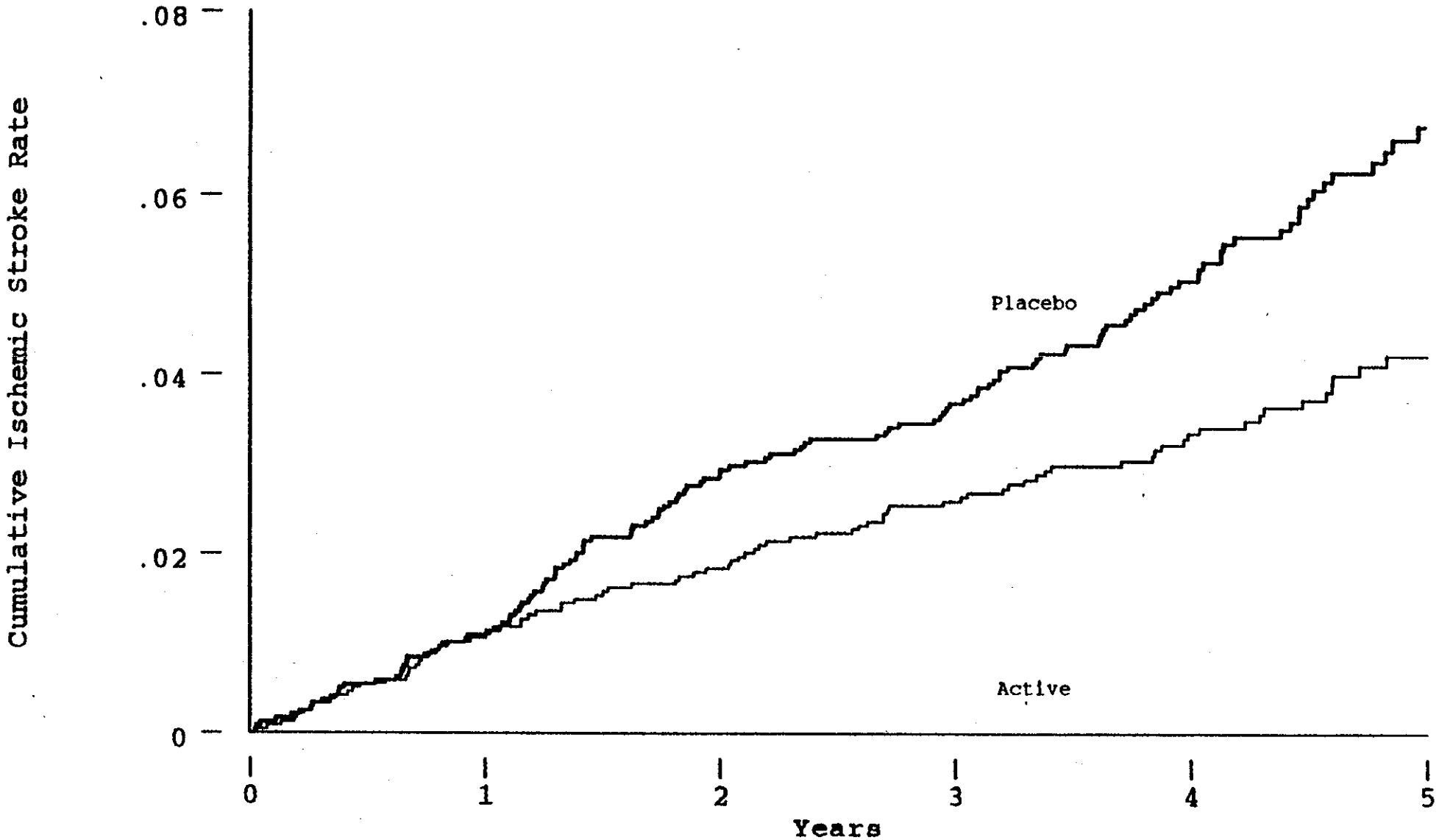
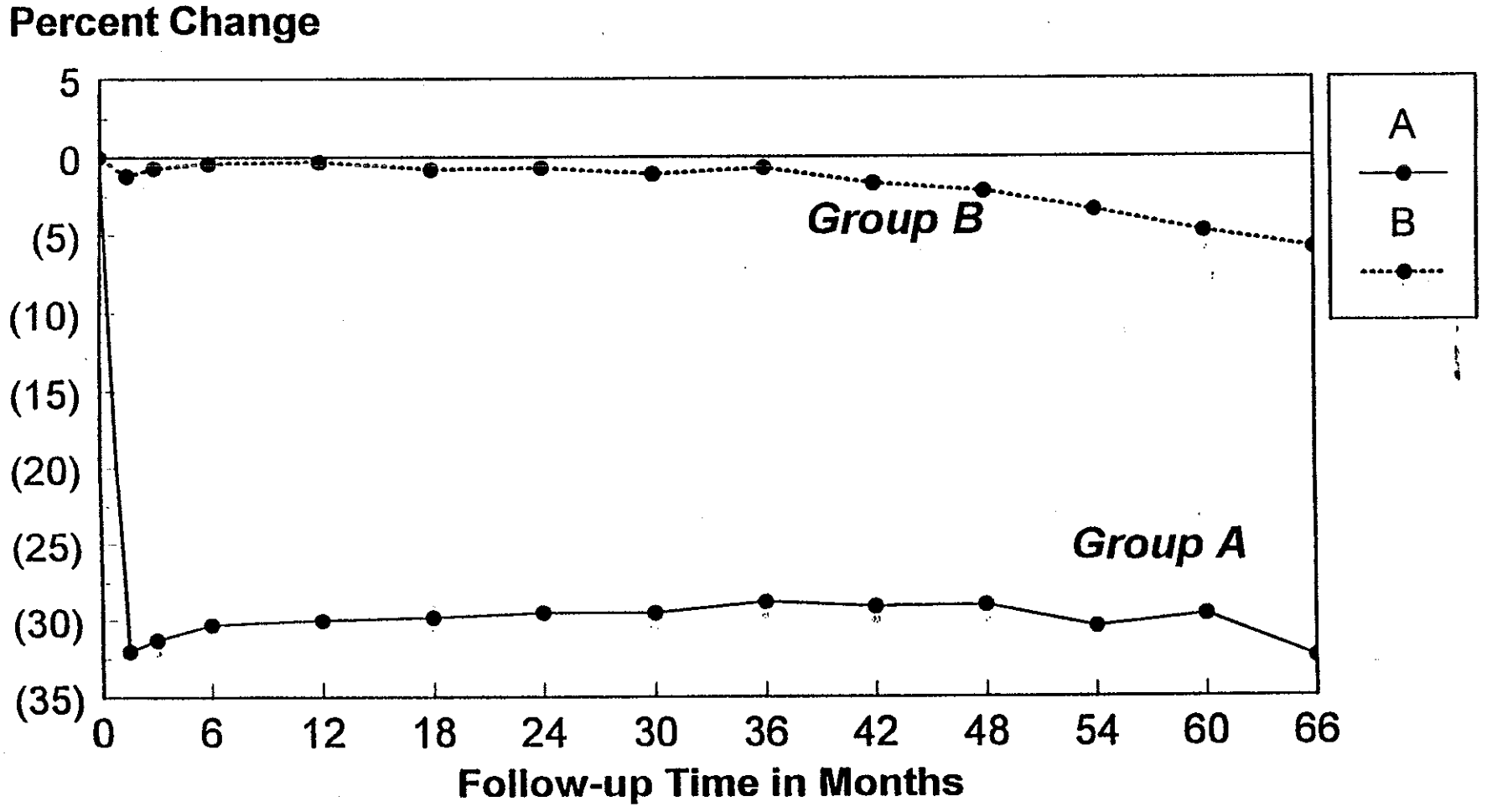


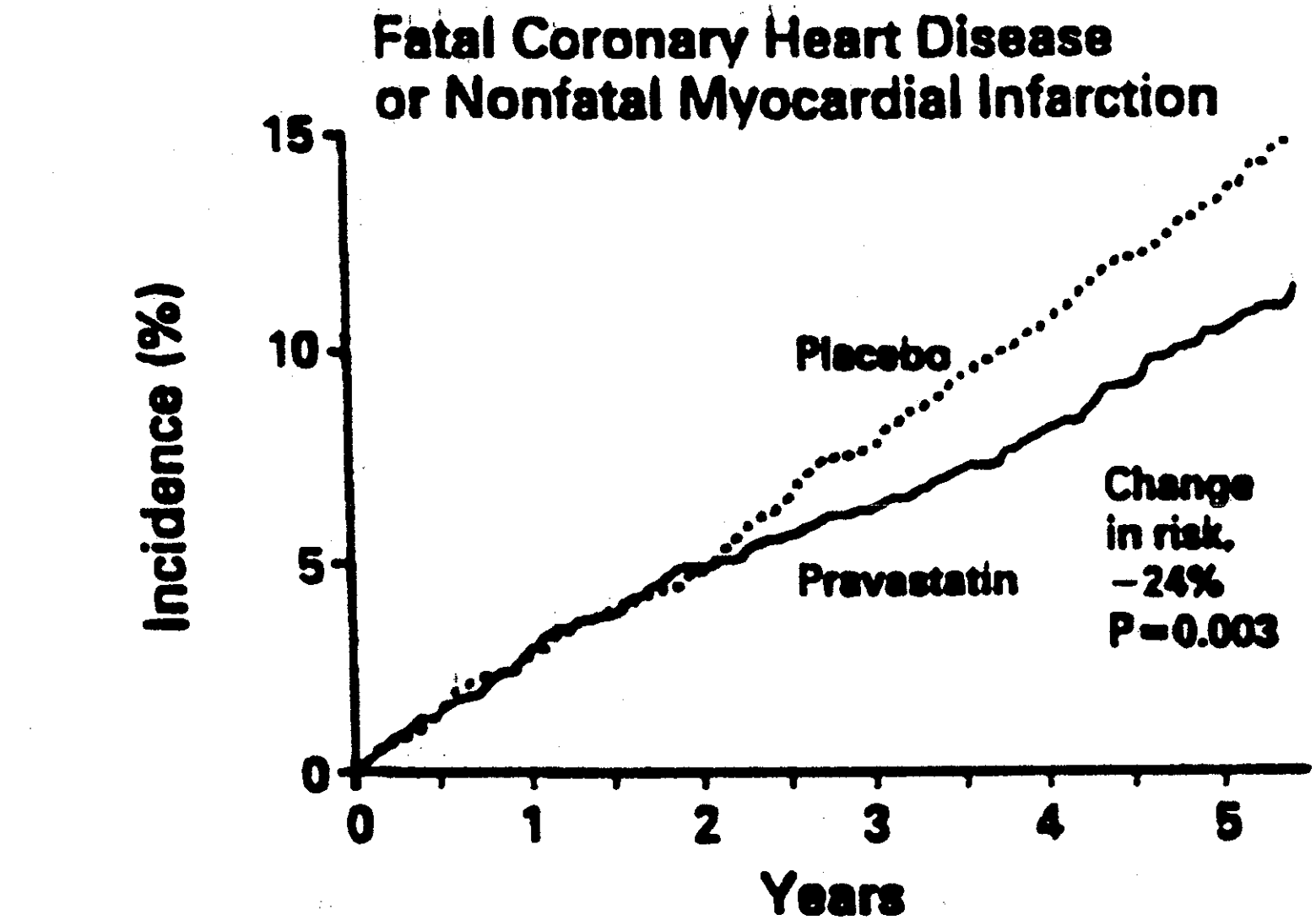

Fig 2.—Cumulative fatal plus nonfatal stroke rate per 100 participants in the active treatment (solid line) and placebo (broken line) groups during the Systolic Hypertension in the Elderly Program.

SHEP - Cum. Ischemic Stroke Rate by Treatment Group



# Figure 1
# Percent Change in LDL from Baseline






| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 2078 | 2009 | 1956 | 1881 | 1810 | 854 |
| Pravastatin | 2081 | 2015 | 1963 | 1915 | 1856 | 900 |

# TREATING TO NEW TARGETS STUDY (TNT)

**"Is there additional benefit in CV risk reduction by treating patients to more aggressive LDL-cholesterol levels?"**

**5-year trial**

**~8600 patients at ~250 sites**

**Two randomized groups**

- **Goal of 100 mg/dl**
- **Goal of 75 mg/dl**

**Primary Endpoint - CHD**

**Uses atorvastatin**

# Surrogate's Status Treatment Dependent

1. CCB - Controversy
   - Case-Control Study
   - Analyses of cohort data
   - Posicor
   - CONVINCE
   - INVEST

2. ACE and diabetics
   - ABCD
   - FACET
   - UKPDS
   - CAPP
   - SHEP

3. JNC VI

4. Non-statins

# National Heart, Lung, and Blood Institute

National Institutes of Health • Public Health Service • U.S. Department of Health and Human Services

EMBARGOED until
4:00 p.m. Eastern
August 22, 1995
(JAMA embargo)

CONTACT: NHLBI Press Office
(301) 496-4236

NHLBI Preparing Statement for Physicians

**CALCIUM CHANNEL BLOCKERS FOR HYPERTENSION**

A case-control study funded by the National Heart, Lung, and Blood Institute (NHLBI) and published in the August 23/30 issue of the *Journal of the American Medical Association* found that high blood pressure patients taking a calcium channel blocker may have a greater risk of heart attack than patients taking a diuretic or a beta blocker.

# ALLHAT and Calcium Channel Blockers

Readers of the *American Journal of Hypertension* may be interested in how the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), recently described in the *Journal*,[1] relates to the controversy over the use of calcium channel blockers to treat hypertension.[2–8] This 40,000 patient trial should provide definitive evidence about the effect on cardiovascular morbidity and mortality of a diuretic (chlorthalidone) and each of three alternative treatments—a calcium channel blocker (amlodipine), an angiotensin converting enzyme inhibitor (lisinopril), and an $\alpha$-adrenergic blocker (doxazosin). Patients 55 years or older with hypertension and at least one other risk factor for myocardial infarction (eg, atherosclerosis or type II diabetes mellitus) will be studied. The purpose of this letter is to address the question of how early the potential superiority of a diuretic to one of the other arms could be detected in ALLHAT.

The New England Journal of Medicine

# Calcium-Channel Blockers for Hypertension — Uncertainty Continues

ALLHAT's Data and Safety Monitoring Board reviews outcome data periodically; the last review was during the fall of 1997 and included a separate evaluation of the primary end point in the subgroup with diabetes. This analysis involved more than 7000 patient-years. According to expected event rates, about three times as many myocardial infarctions should have been observed as in the ABCD trial.[12] The ALLHAT committee recommended that the trial continue according to the protocol and did not accelerate the date of its next review of the data.

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# CONCLUSIONS

- A surrogate marker is not a magic marker

- A correlate does not a surrogate make - Fleming and DeMets, 1996

- One study's endpoint may be another's surrogate
  Wittes, Lakatos, Probstfield, 1989

- ... the suitability of a response variable as a surrogate for [clinical outcome] depends very much on the treatment or interventions under comparison
  Prentice, 1989

- ... this prescription defines a surrogate for a given endpoint in a manner that depends on treatment or treatments under comparison
  Prentice, 1989

# CONCLUSIONS

- Blood pressure appears to be a useful surrogate for outcomes of CHD/stroke/total mortality

- Lipids appear to be a useful surrogate for outcomes of CHD/stroke/total mortality

## HOWEVER

- Surrogate status is treatment dependent

- Interventions may be equivalent with respect to surrogate endpoint but not with respect to clinical outcome and vice versa.

- The surrogate endpoint-clinical outcome relationship may not be linear

- Intervention's effect on outcome may be slow (or very slow) compared to effect on surrogate endpoint

- Subgroups may have different surrogate endpoint-clinical outcome relationships

## PLUS
## THESE CAVEATS FROM
## DeMets and Fleming and others

- Effects on surrogate endpoints may or may not predict clinical outcome

- Intervention may have unintended mechanisms

- Validity of surrogate hard to establish and only after the fact with a particular treatment

- Need an in-depth understanding of causal pathways of disease process

- Surrogate endpoints useful in screening for new therapies Phase II trials

- Always will need to obtain direct evidence about treatment's effect on safety measures and clinical outcomes

- The less time a drug is in clinical trials, the less we know about it. Therefore, the more risk we are taking when making it available.

- Could waste time and effort and patients could be harmed by taking an ineffective or harmful product.